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GUEST EDITORIAL

Surgery and Cancer: Opinion, Evidence, and Proof†

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Fifteen years ago, Vincent de Vita [1], then Director of the National Cancer Institute of the United States, reported in a keynote address on cancer management that 45% of all Americans diagnosed with a potentially fatal cancer in 1980 could now be cured: 28% mainly by surgery, 11% mainly by radiotherapy, and 6% mainly by chemotherapy. Until this century, surgery was the only effective treatment for cancer, which was usually diagnosed at an advanced stage when cures were uncommon. The cure rate for cancer increased from approximately zero in 1900 to about 30% in 1950; prior to World War II, surgery was still the only effective treatment [1]. Therefore, most of the gains in the cure of cancer by surgery were made in the first half of this century, and improvements in the cure rates in the second half have largely come from improvements in radiotherapy and the development of drugs that kill cancer cells (cytotoxic chemotherapy) and/or control their growth (hormones). In Australia in 1995, the 5-year survival for all potentially fatal cancers was about 55% [2], and in the U.S. white population it was about 60% [3]. Most of the additional cures in the last 15 years would not have come from surgery. Whither goest cancer surgery now?

First, surgery and surgeons are in transition, from an era in which individual experience and opinion were the basis of cancer surgery to a new millennium, where levels of evidence or degrees of proof will dominate improvements in cancer cure rates (Table I). In this context, it must be noted that the age-standardized cancer mortality rates for all cancers for men and women in Australia and the United States peaked about 1990 and are now falling [3,5], in part because of public health programs of cancer prevention and early detection. Considerable further gains will be made here; it has been estimated that at least 50% of deaths in developed countries like the United States and Australia are preventable with current knowledge; tobacco and diet are the main preventable causes [6].

There is also potential to improve cure rates and reduce mortality further through earlier diagnosis, and this often results in a surgical procedure as the prime curative modality of treatment. Finally, there will be further improvements in cancer cure rates for screen detected early disease and late diagnosed disease from the intelligent integration of surgery, radiotherapy, and pharmaceutical therapies (multidisciplinary care); the fruits of the molecular genetic revolution will be harvested in the next century. To illustrate how much more we have yet to gain from the application of 20th century knowledge about cancer prevention, early detection, and treatment, and to highlight the ways in which surgery will remain a major factor through the next quarter century, I will briefly consider some of the aspects of control of colorectal cancer (Table II [7–9]).

The Australian Cancer Network has initiated the production of evidenced-based guidelines for the management of colorectal cancer (CRC) in Australia, which will

TABLE I. Levels of Evidence*

Level I	Evidence is obtained from a systematic review of all relevant randomized controlled trials
Level II	Evidence is obtained from at least 1 properly designed randomized controlled trial
Level III	Evidence is obtained from well-designed controlled trials without randomization; or from well-designed cohort or case-control analytic studies, preferably from more than 1 research center; or from multiple time series with or without the intervention
Level IV	Represents the opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

*National Health and Medical Research Council of Australia Guidelines for the Development and Implementation of Clinical Practice Guidelines [4].

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TABLE II. Control of Colorectal Cancer [7–9]

Modalities of control	Level of evidence	Effect on total CRC
Prevention		
High vegetable, fruit, and cereal, low red meat and animal fat diet	III	About 50% preventable
Dietary supplements		
Vitamins, etc.	III	About 50% preventable
Selenium	II	About 50% preventable
Chemoprophylaxis: NSAIDS	III	About 30% preventable
Familial cancer: FAP, HNPCC	III	Up to 3% preventable
Early detection		
FOBT population screening	II	Up to 30% reduction in mortality
Best evidence-based treatment		
Early disease		
Multidisciplinary management (adjuvant systemic therapy or radiotherapy)	I	2–10% increase in cure rates
Total mesorectal excision	III	Local recurrence significantly reduced
Advanced disease		
Chemotherapy	I	Median 6-month increase in survival

cover the spectrum of cancer control from prevention to treatment of advanced disease (Table II). Of particular relevance to surgeons is the likelihood that population screening for CRC using fecal occult blood testing (FOBT) will be introduced in Australia in the near future. Surgeons will have a major role to play in the colonoscopy of FOBT-positive individuals (with consequent polypectomies) and in performing surgery for colonic and rectal cancers. While it is clear that colonoscopies would be shared between surgeons and other specialists, colonic and rectal resection will remain the province of the surgeon.

Population screening for CRC in the low-risk general asymptomatic population aged 50 years or more must include strategies to cope with the 15% or more of individuals who screen positive who will have at least 1 first-order relative who has been diagnosed with the disease (familial bowel cancer). About one fifth of this 15% will be due to the inheritance of any 1 of 7 mutated cancer predisposition genes that cause FAP and HNPCC [10]. Surgeons must work appropriately with familial cancer clinics to ensure optimal management of these individuals and their families, and, in particular, to play a crucial role in surveillance and prophylactic surgery [10]. Population screening must also involve protocols of follow-up of FOBT-positive screenees which are derived from evidence-based guidelines to ensure that the population has access to the optimal curative treatment of early colonic and rectal cancer. There are lessons to be learned from breast cancer management.

By 1976, it was clear that adjuvant systemic chemotherapy in node-positive women who had a mastectomy for breast cancer significantly increased survival [11]. A decade later, the first Australian population breast cancer treatment survey revealed that 13% of premenopausal and 35% of postmenopausal women with node-positive breast cancer had not received any adjuvant systemic treatment [12]. A similar survey in Western Australia in 1989 found that all but 8% of node-positive women had received adjuvant systemic therapy [13], and the second treatment survey in the State of Victoria indicated that by 1990 nearly all node-positive women had received adjuvant systemic treatment [14]. Thus it took at least a decade before Australian women with breast cancer were benefiting fully from knowledge that increased the cure rate of breast cancer gained in the 1970s. Can we do better for CRC?

In 1990, a National Cancer Institute (NCI) consensus conference recommended 5-FU plus levamisole as the standard of care for patients with resected stage III (Dukes C) colon cancer, based on randomized clinical trials reported to 1990 [15]. There have been no published Australian CRC treatment surveys that can reliably inform us of the impact of this recommendation on Australian surgeons. However, a recent report on 477 patients admitted to a community-based Australian hospital in the years 1989–1994 inclusive, found that only 5% of patients with Dukes C colon cancer commenced adjuvant chemotherapy, and only 3% completed a course [16].

The first systematic (Cochrane style) review of the benefits of systemic adjuvant treatment for early breast cancer was only published in 1992 [17], and the first 2 for CRC were published in 1997 [8,9]. These confirm an increased cure rate in Dukes C colon cancer with adjuvant systemic therapy, and also indicate that patients with Dukes B colon cancer could be considered for this treatment, e.g., by participation in a clinical trial. There are currently 2 recommended regimens, 12 months of 5-FU plus levamisole or 6 months of 5-FU plus leucovorin [8], with the balance of evidence favoring the latter [9]. An Australian CRC treatment survey is urgently needed to determine whether adjuvant systemic therapy is now being used appropriately to increase the cure rates of Aus-

tralians diagnosed with colon cancer in 1997. It is hoped that such a survey would show that this has been the case and that Australian surgeons have achieved optimal management of node-positive colon cancer in about half the time it took to achieve this for node-positive breast cancer. For rectal cancer, there is no unequivocal evidence that adjuvant systemic therapy improves survival after resection, although subgroup analyses of randomized controlled trials of colon and rectal cancer indicate that this is likely to be the case [9].

There are at least 2 important aspects of colonic and rectal resection for cancer which remain controversial. Systematic reviews have shown that pre- or postoperative radiotherapy reduces both local recurrence and mortality from rectal cancer (but not all causes mortality) when combined with resection for cure of the disease [9], and 1 randomized controlled trial has shown that preoperative radiotherapy is more efficacious than postoperative radiotherapy [9]. Total mesorectal excision (TME) is claimed to be the new gold standard for curative resection of rectal cancer, with reports from a number of surgical centers of dramatic reductions in local recurrence rates when TME has replaced conventional resection [18]. There are many sources of bias in uncontrolled series, and there is only 1 multiple time series study (level III evidence) that has reported similar results [7]. Will TME obviate the need for radiotherapy? Randomized controlled trials involving TME with or without radiotherapy are planned or have been initiated [18].

Laparoscopic colectomy has been introduced in a number of surgical centers for the treatment of CRC. To data, no randomized controlled trials comparing laparoscopic with conventional colonic resection have been reported. Although laparoscopic surgery for cancer has "face validity," the phenomenon of port recurrence indicates that it is not identical to conventional resection [19]. Prudence (primum non nocere: first do no harm) indicates that its current place in the treatment of CRC should be restricted to randomized controlled trials, where the ethical implications of adverse outcomes have received due attention.

In summary, surgeons will play an increased role in the cure of CRC in the future in the context of prevention, population screening, and improved operations for the cure of early disease. Much of this will be in the context of multidisciplinary management, where medical and radiation oncologists will be essential colleagues. Therefore, in many respects, the treatment of CRC is following the pathway that breast cancer has already trod. All of this takes no account of the 21st century deluge of new pharmaceuticals from the molecular genetics revolution. These will aid in the early detection and treatment for cure of cancer, and the first wave of them is just now breaking upon us. Finally, much of what is happening in the management of CRC and breast cancer will apply to most solid tumors for which surgery is currently a crucial modality of treatment.

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